POST CESSATION FERTILITY AND MENSTRUAL PATTERN AFTER THE USE OF A LONG ACTING INJECTABLE PROGESTOGEN-ESTROGEN COMBINATION

by

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Besides being effective, contraceptives should permit normal resumption of menstrual function and fertility when discontinued. In our experience with Deladroxate (*), a long acting injectable progestogen-estrogen combination, it proved to be fully effective in preventing pregnancy. Not a single pregnancy occurred during 998 treatment cycles in 78 women.

The aim of this investigation is to study the effect of the medication on subsequent fertility and the menstrual patterns of the participants when it is discontinued.

MATERIAL AND METHOD

The present study was carried out on 78 participants who were using a Progestogen-estrogen combination for contraception in the form of monthly injections of Deladroxate for a period of 12—14 months. All were of high parity (average 4.2) with their age ranging between 18 and 40 years (average 30.2). They were followed up monthly during the whole period of medication and for 6 months after ; the menstrual patterns of the participants, before during and after treatment was carefully recorded. The effect of the medication on subsequent fertility was tested in all cases by the number of pregnancies occurring during each post treatment cycle. Pregnancies were

(*) 150 mg 16 alpha, 17 alpha dihydroxy progesterone acetophenide, 10 mg estradiol enanthate.

diagnosed clinically and by the immunologic detection of chorionic gonadotrophins by the Gravindex test. The occurrence of ovulation in a group of 15 cases was determined by an endometrial biopsy obtained on the first day of the menstrual flow of the last treatment cycle and each of the 6 post treatment cycles.

RESULTS

I.—Menstrual Patterns :

1. Cycle length :

The average cycle length of the participants before joining the trial was 26.8 days. During therapy the average was 26.3.

The post treatment average cycle length is shown in Table I.

TABLE I

Post Cessation cycle Length

Cycle	1	2	3	4	5	6
Average duration (days)	29.1	27.5	25.6	25.3	25.4	26.1
Variations	18—48	18—46	20—44	22—37	22—36	23—34

2. Amount of flow :

The average amount of menstrual flow before and during treatment is shown in Table II.

TABLE II

Amount of flow before and during therapy

(Number of cycles per cent)

	Slight	Moderate	Severe	None
Before	12.1	66.7	18.2	3
During	11.7	70.6	12.9	4

Table III shows the change in the amount of flow after stopping medication.

TABLE III

The post cessation amount of menstrual flow

	The incidence per cent					
Cycle	1	2	3	4	5	6
Slight	2.8	1.8	5.1	8.1	9.1	10.6
Moderate	90.1	85.6	84.6	78.9	78.5	77
Severe	5.7	7.2	7.7	7.3	7.4	8.2
None*	1.4	5.4	2.6	5.7	5	4.2

(*) Pregnancies not included.

3. Duration of menstrual flow :

The average duration of menstrual flow for the participants was 4.5 days. This average increased to 8.2 days during therapy. The post cessation figures are shown in Table IV.

TABLE IV

Post Cessation Duration of Menstrual Flow

Cycle	1	2	3	4	5	6
Average duration (days)	6.7	6.1	5.6	5.3	5.4	4.8

4. Intermenstrual Bleeding :

None of the cases was having any intermenstrual bleeding before joining the trial.

During treatment the incidence of break through bleeding (B.T.B.) is shown in Table V.

TABLE V

Spotting and B. T. B. During Treatment

	Incidence per cent
Spotting	0.8
Bleeding	2.8

The incidence of intermenstrual bleeding after stopping therapy is shown in Table VI.

TABLE VI

Post cessation intermenstrual Bleeding

Cycle	1	2	3	4	5	6
Spotting	1.4	1.4	1.8	0	0	0
Bleeding	18.3	17.1	10.2	9.1	7.2	2.1

II.—Subsequent Fertility :

1. Resumption of Ovulation :

The premenstrual biopsies obtained before joining the trial proved that 70% of the participants ovulated during that particular cycle. Biopsies obtained in 15 cases during the last treatment cycle proved that none of them was ovulating.

The results of biopsies obtained in the post cessation period of these 15 cases is shown in Table VII. Three pregnancies occurred in this group, so that 12 biopsies only were obtained at cycle 6.

TABLE VII

The Incidence of Ovulation in The Post Treatment Cycles

Cycle	1	2	3	4	5	6
Number of cases examined	15	14	14	13	12	12
Number of cases with secretory changes	3	3	6	5	7	8

2. **Pregnancies :**

The number of pregnancies occurring during the post treatment cycles is shown in Table VIII. Two of the cases who got pregnant were followed up during the whole period of pregnancy which was uneventful and each normally gave birth at full term to a normal living infant.

TABLE VIII

Post Cessation Pregnancies

Cycle	1	2	3	4	5	6
Number of pregnancies	none	2	4	4	3	2
Cumulative Number	0	2	6	10	13	15
Cumulative incidence per cent	0	2.56	7.68	12.8	16.64	19.20

COMMENT

Fertility subsequent to the use of combined Progestogen-estrogen contraceptives is important, not only as a practical consideration to the women who use them but also as a criterion of their harmlessness to the entire reproductive system.

One of the earlier anxieties over the use of oral contraceptives was the possibility of a decrease in fertility and a change in the menstrual pattern subsequent to prolonged inhibition of ovulation.

As increasing number of women withdrew from oral medication to have further pregnancies, there continued to be encouraging evidence of normal fertility after withdrawal. Goldzieher et al reported a pregnancy rate of 66% in the first post treatment cycles in withdrawals from their trial with different oral contraceptives. In trials carried out under the auspices of the council for the investigation of fertility control, London, 80% of women withdrawing from oral contraceptive medication conceived within two months of stopping. The incidence of abortions and congenital anomalies was found to be almost similar to that occurring in pregnancies not preceeded by oral contraceptive medications.

Tietze reported the results of discontinuing the use of mechanical contraceptives. 34% of women conceived in the first cycle.

In this study the menstrual and fertility patterns subsequent to the use of an injectable long acting progestogen-estrogen combination were presented.

The menstrual patterns were found to be disturbed, particularly during the first three cycles following withdrawal. There was a wide scatter in the variations of cycle lengths which was slightly narrowed in the post treatment cycle four.

The duration of menstrual flow in the first post cessation cycle was one and a half time the pretreatment duration, but it decreased gradually to reach the pretreatment duration at cycle six.

The amount of flow on the other hand was improved on therapy and remained so for the next few cycles.

Intermenstrual bleeding was a real nuisance to participants in the first four cycles after stopping therapy. It was controlled easily in almost all cases by administering one of the oral progestogens daily for 3 to 5 days. In only one case it necessitated curettage.

As regards the resumption of fertility, it was noted that ovulation returns in one third of the cases within 1 to 3 cycles and in two thirds by the 5th and 6th cycles. Taymor (1964) reported that of 15 women

receiving Deladroxate for 6 months two ovulated within two weeks after the last withdrawal bleeding while in the rest there was anovulation and/or amenorrhea which persisted for 1 to 4 months. Rutherford et al (1964) also reported that following 6 months of therapy in 30 women, the first few post treatment cycles seemed predominantly anovulatory.

No pregnancies occurred during the first post treatment cycle. Pregnancies started in the 2nd cycle and continued to occur in the next cycles. An interesting fact was that the percentage of cases ovulating in each cycle was much more than the number of cases who got pregnant.

This stresses the fact that the mechanism by which progestogen-estrogen combinations delays post cessation pregnancy is not simply anovulation and it seems that the other factors, namely, the tubal, endometrial and cervical, which contribute to the antifertility effects of the preparation take a longer time to resume their normal function.

SUMMARY

1. A study of the effect of a long acting injectable contraceptive composed of a progestogen-oestrogen combination (Deladroxate) on subsequent fertility was carried out.

2. 78 multiparous females (18—40 years) were followed up monthly for 12—14 cycles of medication and for 6 months after cessation.

3. Ovulation occurance was determined by endometrial biopsy. Pregnancy was diagnosed clinically and by the immunologic detection of chorionic gonadotrophins by the Gravindex test.

4. The average cycle length was 26.8 days premedicationally & the average cycle length was 26.3 days during therapy. Average cycle length in the first six post cessation cycles was 29.1, 27.5, 25.6, 25.3, 25.4 and 26.1 respectively.

5. The average duration of flow was 4.5 days premedicationally. It was 8.2 days during therapy. After cessation the average duration of flow in the first six cycles was 6.7, 6.1, 5.6, 5.3, 5.4, and 4.8 days respectively.

6. Differences in the amount of flow before and during medication were not significant. Follow-up of the amount of flow in the first six post cessation cycles showed a drop in both heavy and scanty flow and a rise in the percentage of average flow.

7. None of the cases experienced intermenstrual bleeding before medication. Breakthrough bleeding was experienced by 2.8% of cases during medication. After cessation breakthrough bleeding in the first six cycles was 18.3, 17.1, 10.2, 9.1, 7.2 and 2.1% of cases respectively.

8. Endometrial biopsies obtained from 15 cases during the last treatment cycle proved that none of them was ovulating. Post cessation biopsies from those 15 cases in the first 6 cycles showed secretory changes in 3 out of 15, 3 out of 14, 6 out of 14, 5 out of 13, 7 out of 12 and 8 out of 12 cases respectively.

9. None of the cases fell pregnant during medication or during the first post cessation cycle. 2, 4, 4, 3 and 2 pregnancies respectively were encountered from the second to the 6th post cessation cycle. Thus 15 pregnancies occurred during the 6 Post Cessation cycles.

10. Two of the pregnant cases were followed up to term and had normal uneventful pregnancies and deliveries. Both infants were examined after delivery and were found normal.

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